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EXAMINER	
LU, FRANK WEI MIN	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,873	KOPRESKI, MICHAEL S.	
	Examiner	Art Unit	
	FRANK W. LU	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,17-23,25,28-30,33,34,45,46,49 and 50* is/are pending in the application.

4a) Of the above claim(s) *3,7,10,11,19,21,22,30,33,34,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9,12,14,17,18,20,23,25,28,29,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE and the amendment filed on January 12, 2009 have been entered. The claims pending in this application are claims 1-12, 14, 17-23, 25, 28-30, 33, 34, 45, 46, 49, and 50 wherein claims 3, 7, 10, 11, 19, 21, 22, 30, 33, 34, 49, and 50 have been withdrawn due to the restriction requirement and species election mailed on October 18, 2007 and April 21, 2006. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on January 12, 2009. Therefore, claims 1, 2, 4-6, 8, 9, 12, 14, 17, 18, 20, 23, 25, 28, 29, 45, and 46 will be examined.

Claim Objections

2. Claim 1 is objected to because of the following informality: "blood plasma or serum from a human group or population without disease" in lines 8 and 9 of step c) should be "said blood plasma or serum from said human group or population without disease".

3. Claim 5 is objected to because of the following informality: "said non-cellular fraction of blood from a human group or population without disease" in lines 8 and 9 of step c) should be "said non-cellular fraction of blood from said human group or population without disease".

4. Claim 9 is objected to because of the following informality: "blood plasma or serum from a human group or population without cancer" in lines 9 and 10 should be "said blood plasma or serum from said human group or population without cancer".

5. Claim 5 is objected to because of the following informality: "said non-cellular fraction of blood from a human group or population without disease" in lines 11 and 12 should be "said non-cellular fraction of blood from said human group or population without disease".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Scope of enablement

Claims 2 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a product amplified from total extracellular RNA from plasma or serum of a human, does not reasonably provide enablement for performing the methods recited in claims 2 and 6 wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum or non-cellular fraction of blood can be associated with the presence of a neoplastic disease that is characterized by said RNA species in the human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detecting a human RNA species from blood plasma or serum from a human wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human and a method of detecting a human RNA species from a non-cellular fraction of blood from a human wherein the overexpression of a tumor-associated extracellular RNA species in the non-cellular fraction of blood from a human is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claim 2 encompasses a method of detecting a human RNA species from blood plasma or serum from a human wherein the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human and claim 6 encompasses a method of detecting a human RNA species from a non-cellular fraction of blood from a human

wherein the overexpression of a tumor-associated extracellular RNA species in the non-cellular fraction of blood from a human is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human.

The Working Examples

The specification provides working examples (see pages 24-26) for detecting tyrosinase RNA in serum from normal human and a human with malignant melanoma and for detecting c-abl RNA in serum from human.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification teaches to detect tyrosinase RNA in serum from normal human and a human with malignant melanoma and detect c-abl RNA in serum from human (see the specification, pages 24-26), the specification does not provide a guidance to show that the overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 2 and the overexpression of a tumor-associated extracellular RNA species in the non-cellular fraction of blood from a human is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 6. Furthermore, there is no experimental data in the specification to support the claimed invention. During the process of the prior art search, the examiner has not found any prior art which is related to claims 2 and 6.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 2 and the overexpression of a tumor-associated extracellular RNA species in the non-cellular fraction of blood from a human is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 6. Furthermore, there is no experimental data in the specification to support the claimed invention. First, since claims 2 and 6 do not require that neoplastic disease is a specific cancer and it is known that 5T4 is highly expressed in both breast and lung cancers (see Table II in page 92 from Southall et al., Br. J. Cancer, 61, 89-95, 1990) and 5T4 mRNA can be detected in either breast or lung cancer patient serum (see page 172, abstract from Kopreski et al., Annals of the New York Academy of Science, 945, 172-178, 2001), 5T4 mRNA can be considered as a tumor-associated RNA species associated with either breast or lung cancer. When the amplified product or signal of 5T4 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a woman, is detected in an amount or concentration greater than a reference amount or concentration for 5T4 mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a human group or population without said disease, it is unclear how a skilled artisan can determine that a tumor-associated RNA species such as 5T4 mRNA in plasma or serum or a non-cellular fraction of blood of woman is associated with the presence of breast caner in the woman and is

not associated with the presence of lung cancer in the woman as recited in claims 2 and 6. Second, since claims 2 and 6 do not require that neoplastic disease is a specific cancer and it is known that hnRNP-A2/B1 is highly expressed in pancreatic tissues from smokers and pancreatic adenocarcinomas (see page 215, abstract from Yan-Sanders et al., Cancer Letters, 183, 215-220, 2002), hnRNP-A2/B1 mRNA can be considered as a tumor-associated RNA species associated with pancreatic adenocarcinomas. When the amplified product or signal of hnRNP-A2/B1 mRNA, or cDNA therefrom produced from plasma or serum or a non-cellular fraction of blood of a human, is detected in an amount or concentration greater than a reference amount or concentration for hnRNP-A2/B1 mRNA or cDNA therefrom determined from plasma or serum or a non-cellular fraction of blood of a non-smoking human group or population without said disease, it is unclear how a skilled artisan can determine that a tumor-associated RNA species such as hnRNP-A2/B1 mRNA in plasma or serum or a non-cellular fraction of blood of human is associated with the presence of pancreatic adenocarcinomas and is not associated a smoking human.

With above unpredictable factors, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether overexpression of a tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 2 and the overexpression of a tumor-associated extracellular RNA species in the non-cellular fraction of blood from a human is associated with

the presence of a neoplastic disease that is characterized by said RNA species in the human as recited in claim 6.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working example related to the claimed invention recited in claims 2 and 6 and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 4-6, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 or 5 is rejected as vague and indefinite in view of step b). Since the claim does not require that primers or probes specific for a human RNA species or cDNA therefrom have a label which can generate a signal, it is unclear why signal amplifying quantitatively or

qualitatively a portion of the extracted RNA or cDNA therefrom can produce a signal. Please clarify.

11. Claim 2 is rejected as vague and indefinite because it is unclear that overexpression of said tumor-associated extracellular RNA species in the human blood plasma or serum is associated with the presence of a neoplastic disease that is characterized by said RNA species in what. Please clarify.

12. Claim 4 or 8 is rejected as vague and indefinite. Since the claim does not require that a human RNA species or cDNA therefrom is a tumor related RNA or cDNA produced therefrom, it is unclear why the amplified product in step (b) can be produced from a tumor related RNA or cDNA produced therefrom. Please clarify.

13. Claim 6 is rejected as vague and indefinite because it is unclear that overexpression of said tumor-associated extracellular RNA species in the non-cellular fraction of human blood is associated with the presence of a neoplastic disease that is characterized by said RNA species in what. Please clarify.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 4, 5, 8, 9, 12, 20, 23, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* (WO 90/09456, published on August 23, 1990) in view of Korneluk *et al.,* (US Patent No. 6,656,704, priority date: August 5, 1996).

Regarding claims 1 and 4, Balazs *et al.,* teach extracting total extracellular RNA from blood plasma or serum from a human (ie., a cancer patient), amplifying or signal amplifying quantitatively or qualitatively a portion of the extracted RNA or cDNA therefrom to produce an amplified product or signal, using primers or probes specific for a human RNA species or cDNA therefrom (ie., myc), and detecting quantitatively or qualitatively the amplified product or signal as recited in claim 1 wherein the amplified product is produced from a tumor related RNA or cDNA produced therefrom (ie., myc) as recited in claim 4 (see pages 4 and 14-24).

Regarding claims 5 and 8, Balazs *et al.,* teach extracting total extracellular RNA from a non-cellular fraction of blood from a human (ie., a cancer patient), amplifying or signal amplifying quantitatively or qualitatively a portion of the extracted RNA or cDNA therefrom to produce an amplified product or signal, using primers or probes specific for a human RNA species or cDNA therefrom (ie., myc), and detecting quantitatively or qualitatively the amplified product or signal as recited in claim 5 wherein the amplified product is produced from a tumor

related RNA or cDNA produced therefrom (ie., myc) as recited in claim 8 (see pages 4 and 14-24).

Regarding claims 9, 12, and 45, Balazs *et al.,* teach extracting total extracellular RNA from plasma or serum from a human (ie., a cancer patient), a portion of which comprises a human RNA species and determining an amount or concentration of said human RNA species in the extracted portion of human blood plasma or serum as recited in claim 9 wherein the human has cancer as recited in claim 12 and the human has cancer and the RNA species is a tumor-associated RNA (ie., myc RNA) as recited in claim 45 (see pages 4 and 14-24).

Regarding claims 20, 23, and 46, Balazs *et al.,* teach extracting total extracellular RNA from a non-cellular fraction of blood from a human (ie., a cancer patient), a portion of which comprises a human RNA species and determining an amount or concentration of said human RNA species in the extracted portion of a non-cellular fraction of blood from a human as recited in claim 20 wherein the human has cancer as recited in claim 23 and the human has cancer and the RNA species is a tumor-associated RNA (ie., myc RNA) as recited in claim 46 (see pages 4 and 14-24).

Balazs *et al.,* do not disclose comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease wherein the human RNA species extracted from human blood plasma or serum is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amount or concentration of said RNA species or cDNA therefrom extracted from said blood plasma or serum from said human group or population without disease

as recited in claim 1, comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease wherein the human RNA species extracted from a non-cellular fraction of blood is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amount or concentration of said RNA species or cDNA therefrom extracted from said non-cellular fraction of blood from said human group or population without disease as recited in claim 5, and comparing the amount or concentration of said human RNA species from plasma or serum of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as recited in claim 9, and comparing the amount or concentration of said human RNA species from a non-cellular fraction of blood of said human to the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as recited in claim 20.

Korneluk *et al.,* teach to detect expression of hiap-1 in the Raji Burkitt's lymphoma cell line using RT-PCR and determine overexpression of hiap-1 by comparing with positive and negative controls (see column 26).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 or 5 or 9 or 20 by comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease wherein the human RNA species extracted from

human blood plasma or serum is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amount or concentration of said RNA species or cDNA therefrom extracted from said blood plasma or serum from said human group or population without disease or by comparing the detected amplified product or signal to a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease wherein the human RNA species extracted from a non-cellular fraction of blood is determined to be overexpressed when the detected amplified product or signal from the human in an amount or concentration greater than the reference amount or concentration of said RNA species or cDNA therefrom extracted from a non-cellular fraction of blood from a human group or population without said disease or by comparing the amount or concentration of said human RNA species from plasma or serum of said human to the reference range RNA amount or concentration for said RNA species determined from said plasma or serum from said human group or population without cancer or by comparing the amount or concentration of said human RNA species from a non-cellular fraction of blood of said human to the reference range RNA amount or concentration for said RNA species determined from said plasma or serum from said human group or population without cancer in view of the prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because Korneluk *et al.,* have shown to detect expression of hiap-1 in the Raji Burkitt's lymphoma cell line using RT-PCR and determine overexpression of hiap-1 by comparing with positive and negative controls (see column 26) and use of a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human

group or population without disease as an experimental control or the use of a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease as an experimental control or the use of the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control or the use of the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control during the process of performing the method recited in claim 1 or 5 or 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the experimental controls are needed to eliminate alternate explanations of experimental results and used to prevent the effects of one variable from being drowned out by the known, greater effects of other variables. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 1 or 5 or 9 or 20 by using a reference amplified product or signal of said human RNA species or cDNA extracted determined from plasma or serum from a human group or population without disease as an experimental control or using a reference amplified product or signal of said human RNA species or cDNA extracted determined from a non-cellular fraction of blood from a human group or population without disease as an experimental control or using the reference range RNA amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control or using the reference range RNA

amount or concentration for said RNA species determined from plasma or serum from a human group or population without cancer as an experimental control.

Response to Arguments

In page 9, last paragraph bridging to page 17, second paragraph of applicant's remarks, applicant argues that: (1) "[A]n important but subtle distinction must be made in considering what the Balazs reference actually teaches. Specifically in contrast to the teachings of Applicant's specification, the Balazs teachings require the absolute requirement that a nuclease inhibitor (specifically, an RNase inhibitor) be mixed with whole blood prior to separating plasma from the cellular fraction of the blood. Applicant respectfully contends that the Balazs reference cannot be properly understood without considering the teaching in Balazs that a nuclease is required. This is because the consequences of following the Balazs teachings impacts whether what Balazs and Applicant teach are in fact the same, i.e., whether any RNA detected using the Balazs teachings is in fact 'extracellular RNA' as that term is used in Applicant's specification"; (2) "[A]pplicant's specification teaches the presence of extracellular RNA in plasma and serum, irrespective of the addition of an RNase inhibitor. The methods taught in the instant specification do not require addition of an RNase inhibitor prior to separation of plasma. This is because the Applicant recognized, as Balazs and the rest of the art did not, that adding an RNase inhibitor prior to separating the cellular and acellular fractions of blood would stabilize any *intracellular* RNA released from cells during the separation process, and thus provide contaminating intracellular RNA into the plasma sample. One of ordinary skill would recognize this deficiency in the method disclosed in the Balazs reference, and would understand that as a consequence Balazs neither teaches a method that could be used to (unambiguously) detect extracellular RNA in

blood plasma, nor describes the existence of extracellular RNA in blood. The instant inventor found, surprisingly, that extracellular RNA is sufficiently stable even in the purported presence of serum RNases that it can be amplified and detected in human blood plasma or serum without adding RNase inhibitors, as evidenced by detection of extracellular RNA species using the methods disclosed in the instant specification. Adding RNases to blood prior to separating the cellular from the acellular portions thereof is thus not only unnecessary to stabilize extracellular RNA, but can stabilize any artifactually-produced *intracellular* RNA inadvertently released from blood cells during plasma sample separation. Although the Balazs reference recognizes that intracellular RNA contamination should be avoided, its own teachings subvert its intention to avoid detecting these artifactual intracellular RNA species. Balazs fails to provide any way to avoid or overcome the confounding presence of intracellular RNA, and thus provides no teaching that contradicts the understanding in the art as a whole regarding the presence of amplifiable extracellular RNA in plasma. The only source for methods that unambiguously show the extracellular RNA can be detected from blood plasma or serum comes from Applicant's disclosure"; (3) "[A]pplicant respectfully contends that knowledge of a method to amplify and detect *intracellular* RNA extracted from cells, as disclosed by Korneluk et al, would not have provided reasonable expectation that the same method could be applied to *extracellular* RNA from plasma or serum, since the integrity and structure of extracellular RNA in plasma could not be presumed to be sufficiently identical to intracellular RNA. Any presumption that the structure of cellular RNA is the same as RNA that endogenously circulates in plasma as extracellular RNA was without basis at the time of the invention, and is not provided by either the Balazs or the Korneluk references. The expected structural differences between extracellular (substantially

or completely degraded) and intracellular (substantially intact) RNA are supported by subsequent art. RNA endogenously present in plasma has been subjected to apoptotic processes or nucleases, and thus appears to be fragmented or otherwise altered in comparison to cellular RNA. Distinction between cellular RNA and extracellular RNA has recently been noted by Zhou et al (Cancer Letters, 2008, 259:50-60)"; (4) "the Balazs reference affirmatively teaches that amplifiable RNA is only present in plasma when it is from cancer cells, due to the putatively 'special properties' of cancer cells. There is no teaching, and hence no anticipation, that amplifiable mammalian RNA can be detected in plasma from humans without cancer, or when the RNA is not of cancer cell origin"; and (5) "[T]he Korneluk reference does not cure these deficiencies of the Balazs reference. The Korneluk reference is limited to detecting RNA isolated from cancer cells, i.e. *intracellular* RNA, and is completely silent regarding the existence of extracellular RNA. The combination of the Balazs and Korneluk references thus do not render obvious Applicant's invention, since taken together they do not teach detection of extracellular RNA species. Furthermore, the Korneluk reference does not cure the deficiency of the Balazs reference regarding detection of extracellular RNA in the plasma of humans without cancer. Korneluk provides no teaching or suggestion that RNA can be amplified from the plasma of humans without disease. In the absence of any teaching by Balazs or Korneluk that RNA can be amplified from the plasma of humans without disease, and since Balazs specifically teaches away from detecting plasma RNA in any human without cancer, Applicant respectfully contends that it can not be considered obvious to apply a reference range based upon amounts or concentrations of extracellular RNA in the plasma from humans without disease. One skilled in the art would not have had any reasonable expectation that reference amounts or concentrations

of plasma RNA from humans without disease could be defined, since one skilled in the art would have no expectation that RNA could be amplified from the plasma of humans without disease".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the claims do not require extracting total extracellular RNA from plasma or serum in the absence of RNase inhibitor as argued by applicant. Second, applicant has no evidence to show that RNA from human plasma taught by Balazs et al., does not contain extracellular RNA. Third, since Balazs et al., stated that "[S]ince the selected RNase inhibitor does not cause any escape of RNA from the cell before or during their removal" (see page 14, fourth paragraph of the English translation), RNAs from human plasma taught by Balazs et al., must contain extracellular RNA because the selected RNase inhibitor in human plasma prevents intracellular RNA to be release from blood cells before or during blood cell removal. Fourth, although Zhou *et al.,* (Cancer Letters, 2008, 259:50-60) have shown that extracellular RNA is different from intracellular RNA in cultured human gastric cancer cell line, SGC7901 (see pages 50 and 51), since the study from are Zhou *et al.,* was carried out in *in vitro* and indicated that "[H]owever, all of our studies were conducted *in vitro*, and the results can not fully represent the situations in vivo. We should pour into greater efforts to confirm these conclusions by creating in vivo models" (see page 58, right column, last paragraph), and it is known that growth environments in *in vivo* and *in vitro* are different, applicant has no evidence to show that extracellular RNA must be different from intracellular RNA in human plasma or serum. Fifth, although Balazs *et al.,* do not teach that amplifiable mammalian RNA can be detected in plasma from humans without cancer, the rejection is based on the combinations of Balazs *et al.,* and Korneluk *et al.,* and is not dependent on Balazs *et al.,* alone. Sixth, Korneluk *et*

al., is not used to cure these deficiencies of the Balazs reference as argued by applicant but is used to combine with Balazs *et al.,* for the rejection under 35 U.S.C 103. Furthermore, Balazs *et al.,* teach to detect extracellular RNA in human plasma or serum (see above) and extracellular RNA in the plasma of humans without cancer is used as an experimental control which is commonly used to eliminate alternate explanations of experimental results and prevent the effects of one variable from being drowned out by the known, greater effects of other variables.

16. Claims 14 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* in view of Korneluk *et al.,* as applied to claims 1, 4, 5, 8, 9, 12, 20, 23, 45, and 46 above.

The teachings of Balazs *et al.,* and Korneluk *et al.,* have been summarized previously, *supra*.

Balazs *et al.,* and Korneluk *et al.,* do not disclose that the human is a human who has not been diagnosed with cancer as recited in claims 14 and 25.

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 9 or 20 using a human who has not been diagnosed with cancer as recited in claim 14 or 25 in view of prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because use of the plasma or serum or non-cellular fraction from a different human for performing the method recited in claim 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 17, third paragraph bridging to page 18, first paragraph of applicant's remarks, applicant argues that "[A]pplicant respectfully contends that the evidence set forth above establishes that the existence of extracellular RNA in plasma or serum was not in the prior art due to the deficiencies of the cited references. This ground of rejection presumes that the prima facie case of obviousness asserted against the other claims stands, and thus the differences recited in these claims are not sufficient to make them nonobvious. On the contrary, Applicant respectfully contends that the contemporaneous evidence from the art establishes that the Balazs teachings would not be understood to enable the skilled worker to have any reasonable expectation of success in achieving the claimed invention. There could be no reasonable expectation of success on the part of the skilled artisan that methods known to work with intracellular RNA, as disclosed by the Korneluk reference, would be similarly applicable to extracellular RNA. It was not until the teachings of the instant specification that methods for detecting extracellular RNA in the plasma of humans without disease were provided. Applicant thus respectfully contends that this is not an instance where 'prior art elements will perform their

expected function to achieve their expected results,' because the critical element, extracellular RNA, was not a known 'prior art element,' there was no 'expected function' since the status of any such RNA (substantially degraded or substantially intact) was both completely unknown and unpredictable until the instant invention, and thus there were no results to be expected".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, applicant has no evidence to show that RNA from human plasma taught by Balazs et al., does not contain extracellular RNA. Second, since Balazs et al., stated that "[S]ince the selected RNase inhibitor does not cause any escape of RNA from the cell before or during their removal" (see page 14, fourth paragraph of the English translation), RNAs from human plasma taught by Balazs et al., must contain extracellular RNA because the selected RNase inhibitor in human plasma prevents intracellular RNA to be release from blood cells before or during blood cell removal.

17. Claims 17, 18, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balazs *et al.,* in view of Korneluk *et al.,* as applied to claims 1, 4, 5, 8, 9, 12, 20, 23, 45, and 46 above.

The teachings of Balazs *et al.,* and Korneluk *et al.,* have been summarized previously, *supra*.

Balazs *et al.,* and Korneluk *et al.,* do not disclose that the group or population comprises humans of a specific sex or age group as recited in claims 17 and 28 and the group or population comprises humans who smoke as recited in claims 28 and 29.

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 9 or 20 using the group or population comprising humans of a specific sex or age group as experimental controls as recited in claim 17 or 28 or using the group or population comprises humans who smoke as experimental controls as recited in claim 28 or 29 in view of prior art of Balazs *et al.,* and Korneluk *et al.*. One having ordinary skill in the art would have been motivated to do so because use of the plasma or serum or non-cellular fraction from a different group or population as an experimental control for performing the method recited in claim 9 or 20, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 18, third paragraph bridging to page 19, first paragraph of applicant's remarks, applicant argues that: (1) "[A}pplicant asserts the same reasoning and comes to the same conclusions as in his argument with regard to claims 1, 4, 5, 8, 9, 12, 20 and 23 and with regard to claims 14 and 25. The deficiencies of the cited references have been set forth above, and there

are thus no 'expected function' since the status of any such RNA (substantially degraded or substantially intact) was both completely unknown and unpredictable until the instant invention, and thus there were no results to be expected. Furthermore, because the status of RNA in the plasma of humans without disease was completely unknown and unpredictable until the instant invention, there could have been no *expected* results"; and (2) "the Action cites *In re Rose* for the proposition that the combination of old elements cannot be non-obvious in the absence of unexpected results. Applicant notes his argument set forth extensively above, establishing the deficiencies of the Balazs reference that preclude it from supporting the position that extracellular RNA was an 'old element' known in the art. The contemporaneous references cited herein illustrate plainly that the skilled worker did not understand Balazs to teach that stable, intact extracellular RNA could be isolated and amplified from blood plasma or serum. Moreover, the skilled worker would not have understood the cited references to render obvious detecting extracellular tumor-associated RNA in blood plasma or serum from individuals without clinical cancer, and that Applicant's detection thereof was surprising and unexpected. Applicant respectfully contends that the evidence presented herein establishes that the claimed invention is both surprising and unexpected, and that this evidence rebuts the asserted obviousness determination".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, it is proper to reject claims 1, 4, 5, 8, 9, 14, 20, 23, and 25 (see above Response to Arguments related to the rejection items 15 and 16). Second, applicant's statement "the status of RNA in the plasma of humans without disease was completely unknown and unpredictable until the instant invention" is incorrect because early studies have shown that

RNA can be detected in normal blood plasma or serum (see Shutack et al., Journal AOA, 67, 1051-1053, 1968 and Guin et al., Biochemical Medicine, 13, 2224-230, 1975). Third, applicant has no evidence to show that RNA from human plasma taught by Balazs et al., does not contain extracellular RNA. Fourth, since Balazs et al., stated that "[S]ince the selected RNase inhibitor does not cause any escape of RNA from the cell before or during their removal" (see page 14, fourth paragraph of the English translation), RNAs from human plasma taught by Balazs et al., must contain extracellular RNA because the selected RNase inhibitor in human plasma prevents intracellular RNA to be release from blood cells before or during blood cell removal.

Conclusion

18. No claim is allowed.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Frank W Lu /
Primary Examiner, Art Unit 1634
March 19, 2009